REMARKS

Applicants appreciate the time and effort the Examiner spent considering the proposed claims faxed by the Applicants on 08/15/2003 and in working out the proposed claims faxed to the Applicants on 08/27/2003. Applicants have made minor alterations to this claim because the metal ion of proposed claim 1 step a) and the cationic salt of proposed claim 1 step c) are not distinct species. For instance, Na^+ is an example of a monovalent alkali metal ion. Metal ions are typically added to solution as salts, such as NaCl. Applicants have therefore specified a metal cation in steps a), b) and c) of the currently amended claim 1.

A corrected drawing for FIG. 1 is included as requested in the office action.

Applicants now address the office action dated 07/01/2003.

Rejection of the claims under 35 U.S.C. 112.

Claims 1, 20-42 and 46-48 have been rejected under 35 U.S.C. 112 as being indefinite in the recitation of "one or more components of the complex." Applicants have amended the claim 1 to obviate the rejection. Specifically, claim 1 has been amended recite association of the chelator with the polynucleotide. The action further states that it is not apparent how a complex consisting of just a polynucleotide and a chelator can at the same time contain other components. Applicants do not wish to restrict the complex to just a polynucleotide and a chelator. For example, the chelator may be covalently attached to a compound as claimed in claim 26. Association of the chelator/compound with the polynucleotide would then be dependent on association of the chelator with the polynucleotide. This concept is illustrated in the accompanying diagram, where "–○" represents the chelator, and "|" represents a compound which can be attached to the chelator, resulting in "├○".

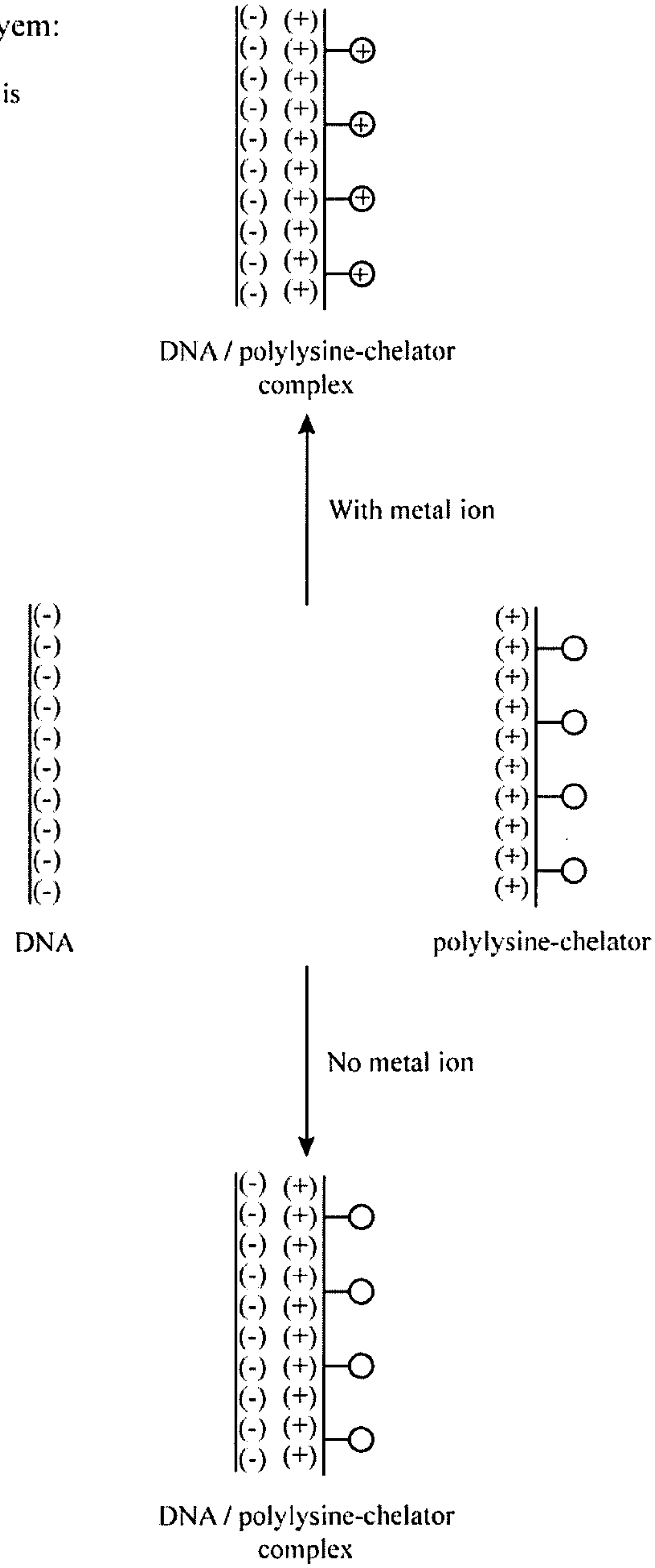
The action suggests on page 3 that claim 38 could be rewritten as "The process of claim 39, wherein the primary amine-containing molecule is covalently linked to the chelator." This amendment to claim 38 would remove a significant embodiment of the claimed invention. The applicants have shown that a chelator that can coordinately bind a primary amine can be used to

associate said chelator with an amine present in a polynucleotide complex. It is important to note that the resulting complex contains at least three components: the polynucleotide, a primary amine-containing molecule in a complex with the polynucleotide, and the chelator. The chelator associates with the complex though non-covalent coordination of an amine by the chelator. Applicants have amended claim 30 to clarify that the complex contains as least three components. To illustrate this concept, a polynucleotide can form a complex with a primary amine containing amphipathic peptide (a releasing signal of claim 39). To this complex an amine coordinating chelator covalently attached to an NLS peptide (cell targeting signal of claim 38) can be added, thereby forming a new complex. The NLS-chelator associates with the polynucleotide/amphipathic peptide complex by coordinately binding primary amines on the amphipathic peptide.

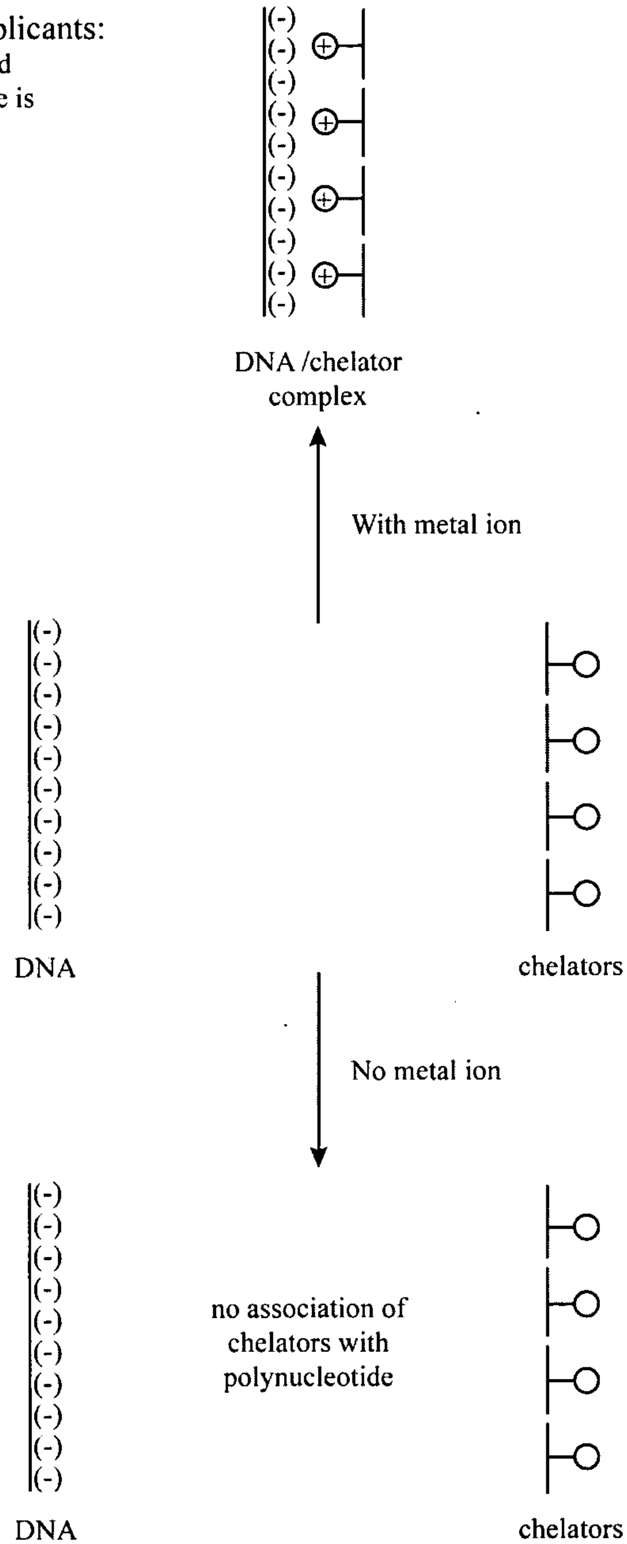
Rejection of the claims under 35 U.S.C. 102:

Claims 1, 20, 22-30 and 32-42 have been rejected under 35 U.S.C. 102(b) as being anticipated or unpatentable over Kayyem. Applicants respectfully disagree. It is the Applicants' opinion that Kayyem teaches association of a polycation with a polynucleotide mediated by ionic interactions between positively charged groups (amines) on the polycation and the negatively charged groups (phosphates) on the polynucleotide. While there are chelating groups covalently attached to the polycation, these chelators do not contribute significantly to the electrostatic interaction of the polycation with the polynucleotide nor are they required for the association of the polycation with the polynucleotide. The interaction between the polycation and the polynucleotide occurs independently of the chelator or any metal ion that may or may not be coordinately bound by the chelator. In other words, the presence of the chelator in the polynucleotide-containing complex is dependent on its covalent linkage to the polycation. Put yet another way, if the chelator of Kayyem is combined with a polynucleotide in a solution that does NOT contain a metal ion that can be bound by the chelator, the chelator will nevertheless be in association with the polynucleotide via the polycation. This association of the chelator with the polynucleotide is indirect by virtue of the chelator being covalently bound to the polycation. Thus, the chelator is associated with the complex in the presence or absence of the metal ion as illustrated below).

Method taught by Kayyem:
association of chelator and delivery of polynucleotide is independent of metal ion



Method taught by Applicants:
association of chelator and delivery of polynucleotide is dependent on metal ion



In contrast, in Applicants' claim 1, combining a chelator with a polynucleotide in a solution that does not contain a metal ion results in no association of the chelator with the polynucleotide. Association of the chelator with the polynucleotide requires the step of adding a positively charged metal ion that can be coordinated (bound) by the chelator. Binding of the metal ion by the chelator imparts positive charge on the chelator which then allows the chelator to electrostatically interact with the polynucleotide. If the metal ion is removed, the chelator and the polynucleotide will dissociate.

In the teaching of Kayyem, removal of the metal ion does not effect the complex formed between the polycation-chelator polymer and the polynucleotide.

Applicants' and Kayyem's teachings contemplate a complex containing a polynucleotide and a chelator. However, Applicants' claim 1 and the teaching of Kayyem differ in a significant aspect. The method of Kayyem requires that the complex contain a polycation and does not teach metal ion dependent association of any chelator with any polymer. Note that Kayyem does not teach a polymer that is cationic only when metal ions are present. While Kayyem does teach that metal ions may be co-delivered with nucleic acid, Kayyem does not teach metal ion dependent enhancement of delivery of polynucleotides to cells.

The action states on page 4 that Kayyem teaches the limitation of recharging the polychelator to change the net charge of the complex. Applicants respectfully disagree. Kayyem teaches that a first polymeric molecule and a second polymeric molecule have opposite charge (page 7, second paragraph). Kayyem further teaches that the first molecule and a third polymeric molecule are also oppositely charged. This third polymeric molecule interacts with the first polymeric molecule. Thus, as taught by Kayyem, the second and third polymeric molecules have the same charge, either both are cationic or both are anionic; and both interact with the first molecule. In contrast, claim 43 recites a first molecule (second polymeric molecule of Kayyem) that interacts with a polynucleotide (first polymeric molecule of Kayyem) and a second molecule (third polymeric molecule of Kayyem) that interacts with the first molecule (second polymeric molecule of Kayyem). Kayyem teaches away from interaction between the second polymeric

molecule (first molecule of instant claim 43) and the third polymeric molecule (second molecule of instant claim 43). Applicants have amended claim 43 to clarify this distinction. Claim 44 of the instant application recites that the second molecule (third polymeric molecule of Kayyem) is a polyanion. A polyanion has the same charge as the polynucleotide (first polymeric molecule of Kayyem) and not an opposite charge.

The action, on page 7 states that "applicant(s) assert that Kayyem does not teach that a metal ion is bound or coordinated by a chelator." This statement is incorrect. Applicants agree Kayyem teaches that a metal ion is bound by the chelator. Rather, applicants assert that the metal ion in the method of Kayyem and the metal ion in the applicants' claims serve different purposes. It is the applicants' opinion that Kayyem does not teach metal ion-dependent association of a chelator with the complex. Instead, Kayyem teaches chelator dependent association of a metal ion with a complex.

The action further states on page 7 that "it would necessarily flow from the teaching of Kayyem that the metal bound chelator enhances a non-covalent, reversible interaction of components of a nucleic acid complex and the cationic polymer complex as claimed." This statement is true, for the teachings of Kayyem, only if the sole component in question–with respect to association with the complex–is the metal ion. The polycation polymer will associate with the polyanion nucleic acid in the presence or absence of the metal ion because the polymer is a polycation in the presence or absence of the metal ion. In contrast, claim 1 of the instant application recites the limitation that the presence of the metal ion is <u>required</u> for the chelator to associate with the polynucleotide.

<u>Rejection of the claims under 35 U.S.C. 103:</u>

Claims 1 and 20-48 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem et al. taken with Hnatowich et al. The action states on page 8 that Hnatowich teaches that it is routine in the art to employ chelators for conjugation to a polymer by ionic bonding. Hnatowich does not teach that a chelator, to which a cation is coordinately bound, can be ionically bound to a polymer through the positive charge imparted on the chelator by the cation.

Hnatowich does not teach that this interaction may be useful in associating the chelator with a nucleic acid to form a complex for delivery of the nucleic acid to a cell. Hnatowich mentions an ionic interaction once; at column 10 line 66 through column 11 line 1. The wording of Hnatowich: "The term 'chelator', as used herein, refers to a moiety that is capable of binding a radionuclide, preferably through non-covalent interactions, e.g. through ionic interactions." Hnatowich, in this statement, is providing a definition of a chelator. The Hnatowich chelator is not ionically associated with a polymer anywhere in this writing.

In contrast, Hnatowich teaches extensively the covalent attachment of chelators to nucleic acid and proteins. (see column 2 lines 64-65; column 3 lines 7-13, 33-37; column 8 lines 40-43; column 10 lines 57-60; column 11 lines 6-9, 42-42, 49-50; column 12 lines 37-40; column 13 lines 7-9; column 14 lines 10-12, 15-17, 42-44; column 16 lines 36-39; and column 25 lines 54-56). Hnatowich teaches only the covalent attachment of a chelator to a nucleic acid and provides no teaching or motivation for cation induced electrostatic interaction of a chelator with any molecule other than the coordinately bound cation. Hnatowich does not, as the action states, teach complexes of nuclei acids associated with a chelator. Hnatowich teaches only a nucleic acid covalently linked to a chelator. Moreover, while Hnatowich teaches that certain polymers can be associated with a DNA-chelator, Hnatowich does not teach that the association is cation dependent.

Applicants acknowledge that the prior art contains examples in which polymers, nucleic acids, and metal ions are present in a formulation intended to be delivered to a cell. However, the applicants have not found any prior where the interaction of the chelator itself with a nucleic acid or polymer or other component of a nucleic acid delivery complex is dependent on binding of a cation by the chelator.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendments and discussion, it is submitted that claims 1, 18-46 are free of the prior art and should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being sent by United States Postal Service Express Mail to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450 on this date: December 12, 2003.

Kirk Ekena